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(56) Documents Cited
GB 1424373 A **WO 92/01696 A1**

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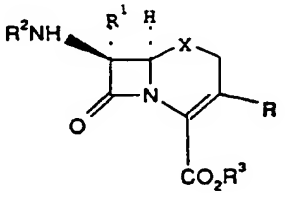
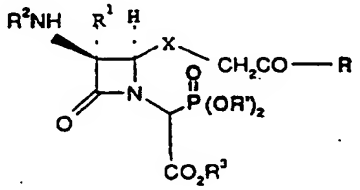
(54) Beta-lactam preparation

(57) A compound of formula (I) or a salt thereof:



(I)

wherein R is a substituent group, R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group (such as a pharmaceutically acceptable in vivo hydrolysable ester group); and X is S,SO,SO_2,O or CH_2, is prepared by base induced cyclisation of a compound of formula (II):



(II)

where R' is alkyl or aryl, and R, R^1, R^2, R^3, R^4, X, and m are as defined in formula (I).

A compound of formula (II) is prepared by reacting the corresponding novel compound in which the $P(=O)(OR')_2$ group is replaced by halogen with a phosphite of formula $P(OR')_3$.

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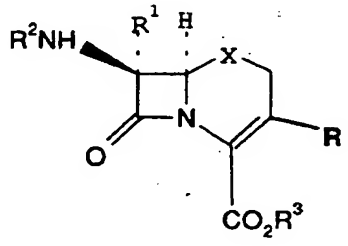
Novel Process

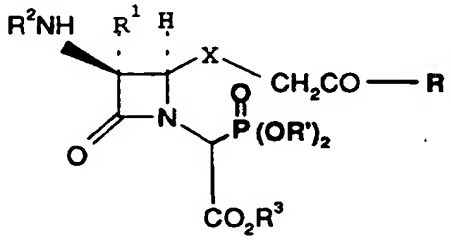
This invention relates to a novel process for preparing β-lactam containing compounds.

The present invention provides a process for the preparation of a compound of formula (I) or a salt thereof:



(I)

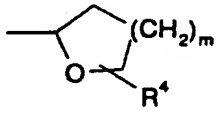
wherein R is a substituent group, R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group, in particular that of an antibacterially active cephalosporin; CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group (such as a pharmaceutically acceptable in vivo hydrolysable ester group); X is S,SO,SO_2,O or CH_2; and m is 1 or 2, which includes the step of base induced cyclisation of a compound of formula (II):



(II)

where R' is alkyl or aryl, and R, R^1, R^2, R^3, R^4, X, and m are as defined in formula (I).

The 3-position substituent group R in formula (I) is suitably an organic group, such as alkyl, e.g. methyl, or aryl, e.g. phenyl, or a cyclic ether group of the general formula:



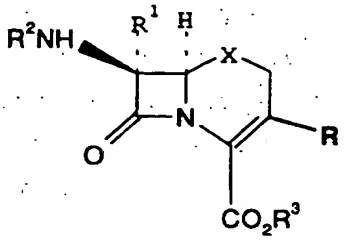
where R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino, CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally

substituted by any other R^4 substituent.

Compounds of formula (I) having such a cyclic ether group as substituent R are disclosed in WO 92/01696. The bonding carbon atom of such a cyclic ether moiety which links the ring to the cephalosporin nucleus in formula (I) is generally asymmetric. The present invention includes processes which produce either stereoisomer, as well as mixtures of both isomers.

In compounds of formula (I) wherein R^1 is formamido, the formamido group can exist in conformations wherein the hydrogen atoms of the -NH-CHO moiety are cis- or trans-; of these the cis- conformation normally predominates.

Since the β-lactam antibiotic compounds of the present invention are intended for use as therapeutic agents in pharmaceutical compositions, it will be readily appreciated that preferred compounds within formula (I) are pharmaceutically acceptable, i.e. are compounds of formula (Ia) or pharmaceutically acceptable salts or pharmaceutically acceptable in vivo hydrolysable esters thereof:



(Ia)

wherein R, R^1, R^2, R^4, m and X are as defined with respect to formula (I) and the group CO_2R^6 is CO_2R^3 where CO_2R^3 is a carboxy group or a carboxylate anion.

Those compounds of the formula (I) wherein R^3 is a readily removable carboxy protecting group other than a pharmaceutically acceptable in vivo hydrolysable ester or which are in non-pharmaceutically acceptable salt form are primarily useful as intermediates in the preparation of compounds of the formula (Ia) or a pharmaceutically acceptable salt or pharmaceutically acceptable in vivo hydrolysable ester thereof.

Suitable readily removable carboxy protecting groups for the group R^3 include groups forming ester derivatives of the carboxylic acid, including in vivo hydrolysable esters. The derivative is preferably one which may readily be cleaved in vivo.

It will be appreciated that also included within the scope of the invention are salts and carboxy-protected derivatives, including in vivo hydrolysable esters, of any carboxy groups that may be present as optional substituents in compounds of formula

(I) or (Ia). Also included within the scope of the invention are acid addition salts of any amino group or substituted amino group that may be present as optional substituents in compounds of formula (I) or (Ia).

Suitable ester-forming carboxyl-protecting groups are those which may be removed under conventional conditions. Such groups for R^3 include benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantyl, 2-benzyloxyphenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, p-toluenesulphonylethyl, methoxymethyl, a silyl, stannyl or phosphorus- containing group, an oxime radical of formula $-N=CHR^7$ where R^7 is aryl or heterocyclic, or an in vivo hydrolysable ester radical such as defined below.

When used herein the term 'aryl' includes phenyl and naphthyl, each optionally substituted with up to five, preferably up to three, groups selected from halogen, mercapto, C_{1-6} alkyl, phenyl, C_{1-6} alkoxy, hydroxy(C_{1-6})alkyl, mercapto(C_{1-6})alkyl, halo(C_{1-6}) alkyl, hydroxy, amino, nitro, carboxy, C_{1-6} alkylcarbonyloxy, alkoxycarbonyl, formyl, or C_{1-6} alkylcarbonyl groups.

The terms 'heterocyclyl' and 'heterocyclic' as used herein include aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or substituted by, for example, up to three groups selected from halogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, halo(C_{1-6})alkyl, hydroxy, carboxy, carboxy salts, carboxy esters such as (C_{1-6})alkoxycarbonyl, (C_{1-6})alkoxycarbonyl(C_{1-6})alkyl, aryl, and oxo groups. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. The term 'heteroaryl' as used herein means a heteroaromatic heterocyclic ring or ring system, suitably having 5 or 6 ring atoms in each ring. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

When used herein the terms 'alkyl' alkenyl, alkynyl and 'alkoxy' include straight and branched chain groups containing from 1 to 6 carbon atoms, such as methyl, ethyl, propyl and butyl. A particular alkyl group is methyl.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine.

A carboxyl group may be regenerated from any of the above esters by usual methods appropriate to the particular R^3 group, for example, acid- and base-

catalysed hydrolysis, or by enzymically-catalysed hydrolysis, or by hydrogenolysis under conditions wherein the remainder of the molecule is substantially unaffected.

Suitable and preferred examples of suitable pharmaceutically acceptable in vivo hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v) disclosed in WO 92/01696.

Examples of suitable in vivo hydrolysable ester groups include, for example, acyloxyalkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1- yl, and (1-aminoethyl)-carbonyloxymethyl; alkoxycarbonyloxyalkyl groups, such as ethoxycarbonyl-oxymethyl, α-ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; dialkyl-aminoalkyl especially di-loweralkylamino alkyl groups such as dimethyl-aminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-(alkoxycarbonyl)-2-alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxy-phthalidyl; and esters linked to a second β-lactam antibiotic or to a β-lactamase inhibitor. A preferred in vivo hydrolysable ester group is the pivaloyloxymethyl ester.

Suitable pharmaceutically acceptable salts of the carboxy group of the compound of formula (I) include metal salts, eg aluminium, alkali metal salts such as sodium or potassium, especially sodium, alkaline earth metal salts such as calcium or magnesium, and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tris-(2-hydroxyethyl)- amine, cycloalkylamines such as dicyclohexylamine, or with procaine, dibenzylamine, N,N-dibenzylethylene- diamine, 1-ephenamine, N-methylmorpholine, N-ethylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, ethylenediamine, or bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with known penicillins and cephalosporins. Other useful salts include the lithium salt and silver salt. Salts within compounds of formula (I), may be prepared by salt exchange in conventional manner.

In compounds of formula (I) or (Ia), the group X may be sulphur or an oxidised sulphur atom, i.e. a sulphoxide (SO) or sulphone (SO_2) group. When X is a sulphoxide group it will be understood that α- and β-isomers may exist; both such isomers are encompassed within the scope of the present invention. Examples of X include S, SO, SO_2 and CH_2. Preferably X is sulphur or CH_2.

Advantageously, R^1 is hydrogen.

Suitably, a cyclic ether at the 3-position of the cephalosporin nucleus is

unsubstituted or substituted by up to three substituents R^4, selected from C_{1-6} alkyl, for example methyl, C_{1-6} alkoxy, for example methoxy, C_{1-6} alkoxycarbonyl for example methoxycarbonyl, C_{1-6} alkoxy C_{1-6} alkyl, for example methoxymethyl, and C_{1-6} alkanoyloxy C_{1-6} alkyl, for example acetoxymethyl. Preferably the cyclic ether at the 3-position of the cephalosporin nucleus is unsubstituted.

Preferably m in such a cyclic ether group is 1.

Preferably such a cyclic ether is bonded to the cephalosporin nucleus at a ring carbon adjacent to the oxygen heteroatom.

Suitable and preferred acyl groups R^2 include those of formulae (a) - (f) disclosed in WO 92/1696.

A preferred group R^2NH - in formula (I) is 2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyiminoacetamino, or a group convertible thereto. For example such a conversion may be via formation of the corresponding 7-amino compound and reaction with the appropriate corresponding acid R^2-OH. Such conversions are standard chemistry and are for example disclosed in WO 92/1696, see for example Example 3 steps (g), (h) and (i) thereof.

It will be appreciated that compounds of formula (I) wherein R^2 is a group of formula (e) (or (f)) can exist as syn and anti (or E and Z) isomers or mixtures thereof. Processes which yield either or both isomers are encompassed within the scope of this invention.

Preferably the compounds of formula (I) wherein R^2 is a group of formula (e) have the syn configuration (i.e. have the group OA_4 syn to the amide linkage) or are enriched in that isomer.

Similarly, when R^2 is a group of formula (f), the group A_4 is preferably cis to the amide linkage, i.e. when group (f) is 2-amino-thiazol-4-yl, the Z-configuration is preferred.

Certain compounds of formula (I) include an amino group which may be protected. Suitable amino protecting groups are those well known in the art which may be removed under conventional conditions without disruption of the remainder of the molecule. Examples of amino protecting groups include C_{1-6} alkanoyl; benzoyl; benzyl optionally substituted in the phenyl ring by one or two substituents selected from C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethyl, halogen, or nitro; C_{1-4} alkoxycarbonyl; benzyloxycarbonyl or trityl substituted as for benzyl above; allyloxycarbonyl,trichloroethoxycarbonyl or chloroacetyl.

Specific compounds of formula (Ia) include the following pharmaceutically acceptable carboxylic acids, salts and in-vivo hydrolysable esters:

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2- (Z)- methoxy-iminoacetamido]-3-[(RS)-tetrahydrofuran-2- yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino-acetamido]-3-[(RS)-tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2- (Z)-methoxy-iminoacetamido]-3-[(RS)-tetrahydropyran- 2-yl] ceph-3-em-4-carboxylate.

(6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyimino-acetamido] -3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylic acid.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z) methoxy-iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z) methoxy-iminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido-3-[(RS)-tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.

Acetoxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino-acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxymethyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-(Z)-pent-2-enamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiadiazol-4-yl)-2-(Z) methoxyimino-acetamido] -3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

(RS)-1-acetoxyethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxy iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

(6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-carboxymethoxyimino acetamido]-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylic acid, disodium salt.

Sodium (6R,7R)-7-[(R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (1S,6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z) methoxyimino acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-l-oxide.

Sodium 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(tetrahydrofuran-2-yl)-1-carba-1-dethiaceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1,1-dioxide.

(RS)-1-(propan-2-yl)oxycarbonyloxyethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl) -2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3-[(5R,5R)-5-methyltetrahydrofuran-2-yl)-ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(furan-2-yl)-2-(Z)-methoxyiminoacetamido] -3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-5,5-dimethyltetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxycarbonyltetrahydrofuran-2-yl)-ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3-[-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

2-ethoxycarbonyl-(Z)-but-2-enyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetomido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

In the compounds of formula (II), R^3 is suitably a p-methoxybenzyl or benzhydryl group. R is suitably alkyl, preferably C_{1-4} alkyl, especially methyl.

Compounds of formula (I) can be prepared in the process of the invention by base included cyclisation of a compound of formula (II) by Wittig-type reaction, preferably a Wadsworth-Emmons cyclisation. The cyclisation is preferably effected by use of a base of formula $M^+ A^-$, where M is an alkali metal cation, and A^- is a strongly basic counter anion, such as butyl lithium, sodium amide, sodium hydride, a sodium alkoxide, or an alkali metal carbonate, e.g. potassium carbonate. Preferably sodium hydride or potassium carbonate is used.

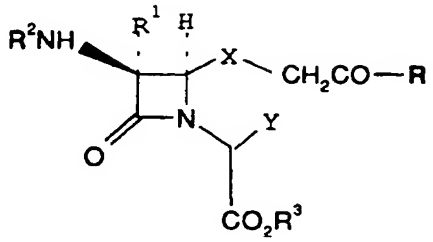
The cyclisation is suitably carried out in an organic solvent, e.g. a hydrocarbon such as toluene using sodium hydride, or acetone using potassium carbonate and will proceed to completion at room temperature but an elevated temperature may be preferable to speed the rate of reaction, and/or to take it to completion.

The temperature required to efffect cyclisation under these conditions is relatively low. Accordingly, fewer impurities or by-products are produced, affording an improved, minimal work-up.

Compounds of formula (I) prepared by the process of this invention may be used to prepare further compounds of formula (I), for example by replacement of protecting groups R^3 with pharmaceutically acceptable salt cations, e.g. sodium, or pharmaceutically acceptable ester groups. Methods of achieving such replacement are described in WO 92/01696.

The present invention also provides a process for the preparation of

phosphonate compounds of formula (II) from compounds of formula (III):



(III)

wherein Y is halogen, the remaining substituents and m being as described for formula (I), by reaction of the compound of formula (III) with a phosphite of formula $P(OR')_3$ where R' is as described in formula (II) above, for example in an Arbuzov type reaction. In this reaction the phosphite may suitably be used as the solvent.

Compounds of formula (III) can be prepared from the corresponding compound of formula (III) in which Y is -OH by treatment with a conventional halogenating agent such as thionyl chloride, e.g. in the presence of a base such as lutidine.

The preparation of compounds of formula (III) in which Y is -OH is described in WO 92/01696, e.g. on pages 25 and 26 and in Example 6(b) thereof.

Compounds of formula (II) in which Y is halogen are believed to be novel, and constitute a further aspect of this invention.

The above and other aspect of the processes of the present invention will now be illustrated further with reference to the following preparative example.

Example 1

4-Methoxybenzyl(6R)-7R)-7-phenylacetamino-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

(a) 4-Methoxybenzyl(2RS)-2-chloro-2-[(3R)-4R)-3-phenyl-acetamino-4-[(RS)-tetrahydrofuran-2-yl-carbonyl methylthio]azetidin-2-on-1-yl]acetate (formula (III)).

4-Methoxybenzyl (2RS)-2-hydroxy-2-[(3R)-4R)-3-phenyl-acetamino-4-[(RS)-tetrahydrofuran-2-yl]-carbonylmethylthio]azetidin-2-on-1-yl]acetate was prepared as in Example 6(b) of WO 92/01696. A solution of the compound (1.355g, 2.5mmol) in dry tetrahydrofuran (10ml) was cooled to -15°C. 2,6-lutidine (0.267g, 2.5mmol) was added, followed dropwise by a solution of thionyl chloride (0.297g, 2.5mmol) in tetrahydrofuran (5ml). After the addition, the mixture was stirred for 15 minutes while the temperature rose to 0°C. The lutidine hydrochloride was filtered off and

the filtrate evaporated *in vacuo* to provide the title compound as a foam.

(b) Dimethyl (4-methoxybenzyloxycarbonyl) [(3R)-4R)-3-phenyl-acetamino-4-[(RS)-tetrahydroxyfuran-2-yl-carbonyl methylthio]azetidin-2-on-1-yl)methylphosphonate (formula (II).

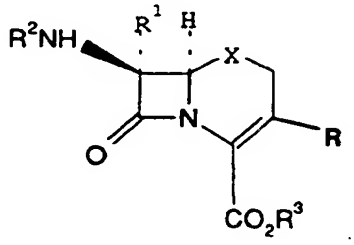
The compound obtained in (a) above was dissolved in trimethylphosphite (10ml) and warmed to 90°C for 30 minutes. Excess phosphite was removed *in vacuo* then the residue dissolved in ethyl acetate (20 ml) and washed with water (4 x 10ml). After drying over magnesium sulphate, the solution was concentrated and chromatographed on silica gel eluting with ethyl acetate to give the title compound as a pale yellow foam (0.712g, 45%).

(c) (4-Methoxybenzylcarbonyl) [(6R)-7R)-7-phenylacetamino-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate (formula (I)).

A solution of the compound obtained in (b) above (0.158g, 0.25mmol) in dry toluene (5ml) was added dropwise to a stirred suspension of sodium hydride (0.01g of 60% dispersion in oil, 0.25 mmol) in dry toluene (5ml). After stirring at ambient temperature for 1 hour the mixture was warmed to 80° for 1 hour then cooled and washed with water (2 x 5ml). The pale yellow solution was dried ($MgSO_4$) and rapidly chromatographed on silica gel eluting with 25% hexane in ethyl acetate, to give the title compound (0.064g, 50%).

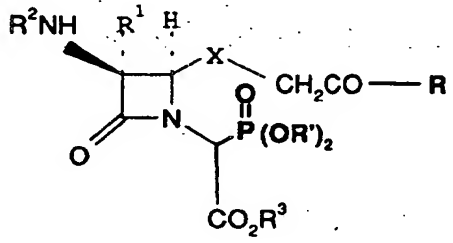
What we shall claim may include the following:-

1. A process for the preparation of a compound of formula (I) or a salt thereof:



(I)

wherein R is a substituent group, R^1 is hydrogen, methoxy or formamido; R^2 is an acyl group; CO_2R^3 is a carboxy group or a carboxylate anion, or R^3 is a readily removable carboxy protecting group (such as a pharmaceutically acceptable in vivo hydrolysable ester group); X is S,SO,SO_2,O or CH_2; and m is 1 or 2, which includes the step of base induced cyclisation of a compound of formula (II):



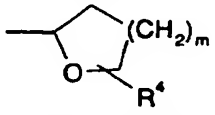
(II)

where R' is alkyl or aryl, and R, R^1, R^2, R^3, R^4, X, and m are as defined in formula (I).

2. A process according to claim 1 wherein the 3-position substituent group R in formula (I) is an organic group.

3. A process according to claim 2 wherein the 3-position substituent group R in formula (I) is alkyl or aryl.

4. A process according to claim 2 wherein the 3-position substituent group R in formula (I) is a cyclic ether group of the general formula:



where R^4 represents hydrogen or up to four substituents selected from alkyl, alkenyl, alkynyl, alkoxy, hydroxy, halogen, amino, alkylamino, acylamino, dialkylamino,

CO_2R, $CONR_2$, SO_2NR_2 (where R is hydrogen or C_{1-6} alkyl), aryl and heterocyclyl, which may be the same or different and wherein any R^4 alkyl substituent is optionally substituted by any other R^4 substituent.

5. A process according to any one of the preceding claims wherein the compound of formula (I) is selected from the compounds:

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2- (Z)- methoxy-iminoacetamido]-3-[(RS)-tetrahydrofuran-2- yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino-acetamido]-3-[(RS)-tetrahydropyran-2-yl]ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2- (Z)-methoxy-iminoacetamido]-3-[(RS)-tetrahydropyran- 2-yl] ceph-3-em-4-carboxylate.

(6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-hydroxyimino-acetamido] -3-[(RS)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylic acid.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z) methoxy-iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Pivaloyloxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z) methoxy-iminoacetamido]-3-[(R)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido-3-[(RS)-tetrahydrofuran-3-yl]ceph-3-em-4-carboxylate.

Acetoxymethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyimino-acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxymethyltetrahydrofuran-2-yl)ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-(Z)-pent-2-enamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiadiazol-4-yl)-2-(Z) methoxyimino-acetamido] -3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

(RS)-1-acetoxyethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxy iminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

(6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-carboxymethoxyimino acetamido]-3-[(RS)-tetrahydrofuran-2-yl]-ceph-3-em-4-carboxylic acid, disodium salt.

Sodium (6R,7R)-7-[(R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (1S,6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z) methoxyimino acetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1-oxide.

Sodium 7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(tetrahydrofuran-2-yl)-1-carba-1-dethiaceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate-1,1-dioxide.

(RS)-1-(propan-2-yl)oxycarbonyloxyethyl (6R,7R)-7-[2-(2-aminothiazol-4-yl) -2-(Z)-methoxyiminoacetamido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3-[(5R,5R)-5-methyltetrahydrofuran-2-yl)-ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(furan-2-yl)-2-(Z)-methoxyiminoacetamido] -3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-[(S)-5,5-dimethyltetrahydrofuran-2-yl]-ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido]-3-(5-methoxycarbonyltetrahydrofuran-2-yl)-ceph-3-em-4-carboxylate.

Sodium (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetamido] -3-[-methyltetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

2-ethoxycarbonyl-(Z)-but-2-enyl (6R,7R)-7-[2-(2-aminothiazol-4-yl)-2-(Z)-methoxyiminoacetomido]-3-[(S)-tetrahydrofuran-2-yl]ceph-3-em-4-carboxylate.

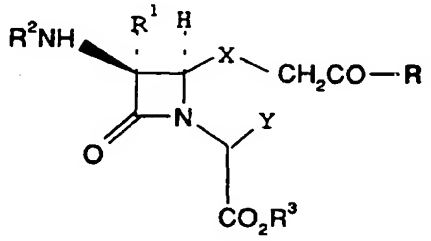
6. A process according to any one of the preceding claims wherein the cyclisation is effected by use of a base of formula $M^+ A^-$, where M is an alkali metal cation, and A^- is a strongly basic counter anion

7. A process according to claim 6 wherein the base is selected from butyl lithium, sodium amide, sodium hydride, a sodium alkoxide, or an alkali metal carbonate.

8. A process according to claim 7 wherein the base is selected from sodium hydride and potassium carbonate.

9. A process according to claim 8 wherein the cyclisation is carried out in toluene as solvent using sodium hydride as the base, or in acetone as solvent using potassium carbonate as the base.

10. A process for the preparation of phosphonate compounds of formula (II) from compounds of formula (III):



(III)

wherein Y is halogen, the remaining substituents and m being as described for formula (I), by reaction of the compound of formula (III) with a phosphite of formula $P(OR')_3$ where R' is as defined in formula (II) above.

11. A compound of formula (II) as defined in claim 10 in which Y is halogen.

12. A process according to any one of the preceding claims, substantially as hereinbefore described with reference to Example 1.

The Patent Office

Application No:	GB 9510126.7	**Examiner:**	Peter Davey
Claims searched:	1-9	**Date of search:**	1 July 1996

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C (CKE)

Int Cl (Ed.6): C07D 501/02 501/08

Other: Online: WPI, CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB1424373	(MERCK), see eg. page 4, lines 26-30	1 at least
A	WO 92/01696 A1	(BEECHAM), see eg. pages 23-24	1 at least

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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